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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Stefan Dietmar Anker and Andrew Justin Stewart Coats

Serial No: 09/807,558 Art Unit: 1647

Filed: July 17, 2001 Examiner: Fozia M. Hamud

For: *METHODS OF TREATMENT*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

We, Stefan Dietmar Anker and Andrew Justin Stewart Coats, hereby declare that:

1. We are inventors of the above-identified application.

3. We have reviewed the Office Action mailed May 16, 2005 in the above-identified application.

4. We understand that claims 1-4, 19 and 29-31 were rejected under 35 U.S.C. 112, first paragraph, on the basis that the specification does not enable those of skill in the art to make and use the claimed methods for treatment of cachexia by administering to a patient an agent that reduces sympathetic nervous system activity. The following experiments demonstrate that the claimed methods are enabled for one of ordinary skill in the art as of the time we filed the parent application, October 15, 1998.

5. One of ordinary skill in the art as of 1998 would have been a physician or a Ph.D. working in the field of beta receptors.

6. Using the guidance set forth in the specification as filed, we have analyzed results from the trial reported in Packer, et al., *N. Engl. J. Med.* 344(22):1651-1658 (2001), a copy of which is enclosed. In this trial 2289 patients who had symptoms of heart failure at rest or on minimal exertion, who were clinically euvolemic, and who had an ejection fraction of less than 25 percent were randomized in double-blind fashion, 1133 patients to placebo and 1156 patients to treatment with carvedilol (starting at 3.125 mg and uptitrating to 25 mg twice a day as tolerated) for a mean period of 10.4 months, during which standard therapy for heart failure was continued. A worthwhile increase in body weight was only seen in the subset of patients who had cachexia and was not seen in other patients who did not have cachexia. This demonstrates that the weight gain effect of the beta blocker was not via an improvement in heart failure, but was specific to an effect on cachexia. Fewer patients in the placebo group (n=167) than in the carvedilol group (n+235) had a weight gain of $\geq$ 5%, reflecting a 40% greater overall chance of a clinically significant weight gain with carvedilol (P+0.003). In addition a significantly greater weight gain compared to placebo was seen only in those patients who were cachectic at baseline (defined as BMI<22) (P+0.0001). In the patients who were cachectic at baseline a weight gain of 5% was seen in 44% of patients receiving carvedilol compared to only 24% of those receiving placebo (see Table 1). For those heart failure patients who were not cachectic at baseline (the latter three columns of Table 1) no significant difference was seen in the numbers of patients gaining weight

between those who received carvedilol compared to those who received placebo. This demonstrates that the beta blocker only produced beneficial weight gain in patients who had cachexia.

7. We have also analyzed the results form Mahe, I., "The ELITE-2 study" *Presse Med.* Sep 9; 29(25):1407 (2000). A copy of the summary of the study as analyzed is enclosed. The enclosed summary shows that beta receptor blockers reduce weight loss in the subgroup of patients with chronic obstructive pulmonary disease (COPD) independent of the degree of cardiac dysfunction (LVEF) and the degree of severity (NYHA class) (see pages 7-9). The study also shows that spironolactone/aldactone reduces weight loss independent of the degree of cardiac dysfunction (LVEF) and the degree of severity (NYHA class) (see pages 1-3). New data on spironolactone and weight gain in the COPD subgroup of cardiac heart failure (CHF) patients is provided (see pages 4-6). These results demonstrate that an aldosterone antagonist is effective in causing weight gain in patients with COPD, when typically in heart failure it is supposed to decrease weight gain since it is also a diuretic.

8. We have also studied the effect of the erythropoietin analogue, darbepoietin alpha in 41 cachexia patients with heart failure (19 receiving active darbepoietin alpha and 22 receiving matching placebo in a double-blind randomized controlled trial). Patients on placebo lost weight, an effect prevented by darbepoietin alpha (see Table 2). This treatment was reported to have no significant effect on heart failure. These results demonstrate that treatment with the erythropoietin analogue, darbepoietin alpha, had a clear effect on cachexia but did not affect the

underlying disease, heart failure.

9. We confidentially requested a colleague, Dr. Piotr Ponikowski, to conduct the following experiment. Dr. Ponikowski treated three patients with cachexia due to cancer, a non-cardiovascular illness, with beta-blockers and spironolactone (an aldosterone antagonist) and reported the results discussed below to us on August 6, 2005.

10. Patient A. Patient A was a 71-year old male, hypertensive patient diagnosed with prostate cancer. His hypertension was well-controlled with amlodipine and diuretic therapy. He had no symptoms of heart failure. He was suffering from weakness, shortness of breath and weight loss of about 6-7 kg over a period of 8-9 months. His weight prior to treatment was 71 kg and body mass index (BMI) was 22.4. Bisoprolol treatment for cachexia was started at 5 mg o.d., which was increased within a month up to 10 mg o.d. During treatment his blood pressure was well controlled and his resting heart rate dropped slightly. During treatment his weight increased 4.5 kg in the first 4 month and an additional 2 kg was gained over the following 3 months. His weight at the time of the report was 78 kg. The treatment with bisoprolol also resulted in an increased appetite and no shortness of breath.

11. Patient B. Patient B was a 59-year old female diagnosed with coronary artery disease and breast cancer. She had no symptoms of angina and her left ventricle function was well preserved. She was taking Asacol, 75 mg o.d., atorvastatin, 10 mg o.d., and nitroglycerin. She was suffering from weakness and weight loss of about 5 kg over a period of 6 months. Her weight prior to treatment was 58 kg and BMI was 22.4. Treatment with carvedilol was given

6.25 mg twice daily up to 12.5 mg twice daily. Her blood pressure was well controlled and her resting heart rate dropped slightly. During treatment she experienced weight gain of 3.5 kg in the first 4 months. Her weight at the time of the report was 61 kg. Her appetite also improved and she experienced no shortness of breath.

12. Patient C. Patient C was a 75-year old, hypertensive male patient diagnosed with gastric cancer. He experienced no clinical symptoms of heart failure and was suffering from severe weakness, shortness of breath, and weight loss of about 8 kg in a period of about 12 months. His weight prior to treatment was 75 kg. He was treated with spironolactone at a dose of 25 mg o.d. which was increased within a month up to 50 mg o.d. During treatment his blood pressure was well controlled and there were no changes in his resting heart rate. During treatment he gained 3 kg in the first 3 months and an additional 1 kg over the next 3 months. He also started feeling better and his shortness of breath and weakness improved.

13. These results demonstrate that patients with cachexia can effectively be treated with sympathetic nervous system effectors such as beta-blockers and aldosterone antagonists.

14. In summary, the data discussed in this Declaration demonstrate that patients with cachexia can effectively be treated as described in the specification with compounds described in the specification that reduce sympathetic nervous system activity.

15. We declare that all statements made herein of our own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or

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imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 3rd Oct 2005 Stefan Dietmar Anker

Date: Sept 27 2005 Andrew Justin Stewart Coats

TABLE 1. Frequency of Weight Gain and Weight Loss

	Baseline Body Mass Index (kg/m^2)			
	<22	22-<25	25-<30	≥30
Weight Gain ≥5%				
Carvedilol	60/136 (44%)	63/265 (24%)	74/453 (16%)	37/232 (16%)
Placebo	30/125 (24%)	50/278 (18%)	58/430 (13%)	29/229 (13%)
HR (95% CI)*	2.20 (1.41-3.43)	1.23 (0.85-1.79)	1.11 (0.79-1.57)	1.48 (0.91-2.41)

*HR denotes carvedilol:placebo hazard ration, CI is confidence interval.

TABLE 2. Effect of Erythropoietin Analogue on Body Weight

BODY WEIGHT	
Mean (±) changes form baseline to week 27	
Placebo	-1.2 ±0.7 kg
Darbepoetin alpha	+0.1 ± 1.1 kg